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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,883	05/14/2001	Lex M. Cowsert	ISPH-0576	9012

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,883	COWSERT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,25,26,29-32,37,38,41-47,49 and 51-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,25,26,29-32,41-47,49 and 51-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5-19-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communications filed 5-19-04.

Claims 22, 25, 26, 29-32, 37, 38, 41-47, 49, 51-74 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 2-13-04 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

The allowability of claims 22, 25, 26, 29-32, 41-47 and 49 is withdrawn in light of the new rejection set forth below.

Claims 22, 25, 26, 29-32, 37, 38, 41-47, 49, 51-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro (i.e. acellular) inhibition of human PTP1B comprising the

administration of antisense that specifically target SEQ ID NO: 243, and being enabling for the in vitro cellular and in vivo inhibition of PTP1B comprising the administration of antisense between 8-50 nucleobases that target SEQ ID NO: 3, does not reasonably provide enablement for treatment in a mammal comprising the in vivo administration of antisense that target and inhibit the genomic nucleic acid of SEQ ID NO: 243. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods of treating diseases or conditions in an organism comprising the administration of antisense in vivo that target and inhibit the genomic nucleic acid of SEQ ID NO: 243.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. A subset of these references have been provided in the prior Office action mailed 11-7-02. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). Additionally, Palu et al teach that the success of gene

delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.)

Peracchi cautions investigators about the problems of achieving in vivo efficacy using oligonucleotide based approaches: "Much progress has been made towards understanding the structure and mechanism of these catalysts [ribozymes]...Despite this, it is not yet clear whether these molecules can be developed into clinically useful pharmaceutical preparations." (See the abstract on page 47). Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (See text on page 51).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (see especially pages 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense

effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The targeting of genomic DNA located in the nucleus, as opposed to mRNA or pre-mRNA located in the cytoplasm, requires overcoming additional hurdles of sufficient subcellular targeting and delivery of oligonucleotides, as well as additional steric hindrances due to the higher order structure of eukaryotic genomic DNA (e.g. in nucleoprotein complexes including histones) (see Stein et al Science 261: 1004-1012 at 1006, 3rd paragraph). Homes et al (Nucleic Acids Res. 25(4): 769-775 at 769) studied hammerhead ribozyme efficacy in target gene inhibition, stating the "co-localization of the ribozyme with its target, i.e. the subcellular distribution of ribozymes, is assumed to be crucial for efficacy."

Homes et al microinjected ribozymes directly into the nucleus of target cells in vitro in order to deliver sufficient concentrations of oligonucleotides for nuclear target gene inhibition (see pages 769-770).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating or delaying the onset of conditions or diseases associated with PTP1B comprising the administration of antisense oligonucleotides which specifically target any region and inhibit the expression of the genomic nucleic acid of SEQ ID NO: 243 encoding PTP1B. The specification teaches the inhibition of mRNA SEQ ID NO: 3 (encoding PTP1B) expression in vitro in various target cell lines and in a Type 2 diabetes mouse model (db/db) comprising the intraperitoneal administration of antisense between 8-50 nucleobases, whereby blood and plasma glucose levels were decreased in this Type 2 diabetes model upon inhibition of PTP1B expression, and further whereby body weight gain was comparable to wild type body weight gain upon inhibition of PTP1B expression in treated db/db mice. The specification fails to teach the targeting and inhibition of the genomic sequence of PTP1B, SEQ ID NO: 243, in cells in vitro or in an organism using antisense, and further whereby treatment effects are provided. The specification teaches the cellular targeting and inhibition of cytoplasmic mRNA encoding PTP1B of SEQ ID NO: 3. The specification also teaches the in vitro targeting and inhibition of the selected regions of the genomic SEQ ID NO: 243 (as shown in Tables 3 and 4, pages 91-95 of the instant specification) in a cell free assay.

One skilled in the art would not accept on its face the examples given in the specification of the inhibition of PTP1B of (cytoplasmic) mRNA of SEQ ID NO: 3 in vitro, in various cell lines and in vivo as being correlative or representative of the successful targeting and inhibition of the entire genomic sequence of SEQ ID NO: 243 in cells in vitro or in vivo, and further whereby treatment effects are provided in a mammal in view of the lack of guidance in the specification and known unpredictability associated with the ability to target the nucleus and provide sufficient quantities of antisense oligonucleotides in that subcellular organelle for targeting and inhibiting genomic DNA using antisense in target cells in vitro or in vivo, or the known lack of ability to predict the efficacy of antisense targeting any genomic sequence in treating any conditions or diseases in an organism. The conditions required for sufficient nuclear delivery and uptake of antisense, and the conditions required for antisense to bind to the intended nuclear target sequence under cellular conditions requires experimentation beyond that provided in the instant specification. Cell free conditions for genomic DNA targeting by antisense are not necessarily correlative or representative of the ability to target and inhibit genomic DNA under conditions existing in the nucleus of cells (e.g. the genomic target sequence can be masked by higher order DNA structure or by nucleoprotein complexes; sufficient subcellular concentrations must be delivered to the nucleus). The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate nuclear delivery in vitro, or in vivo delivery and treatment effects provided by antisense

targeting any region of the genomic DNA of SEQ ID NO: 243 in an organism following the inhibition of genomic sequence of SEQ ID NO: 243.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to compositions and methods of treating diseases or conditions in an organism comprising the administration of antisense in vivo that target and inhibit any region of the genomic nucleic acid of SEQ ID NO: 243. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites of genomic DNA under cellular conditions, and modes of delivery and formulations to target the nucleus of appropriate cells and /or tissues harboring the genomic PTP1B of SEQ ID NO: 243, such that PTP1B expression is inhibited in the nucleus of cells in vitro or *in vivo,* and further that treatment effects are provided in that organism. Since the specification fails to provide any particular guidance for the successful targeting and inhibition of the entire genomic sequence of SEQ ID NO: 243 in cells in vitro or in vivo whereby treatment effects are provided in an organism, and since determination of these factors for a particular target genomic sequence in appropriate target cells in an organism is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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7-5-04

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